ORIGINAL ARTICLE

Five-Year Risk of Stroke after TIA or Minor Ischemic Stroke

P. Amarenco, P.C. Lavallée, L. Monteiro Tavares, J. Labreuche, G.W. Albers, H. Abboud, S. Anticoli, H. Audebert, N.M. Bornstein, L.R. Caplan, M. Correia, G.A. Donnan, J.M. Ferro, F. Gongora-Rivera, W. Heide, M.G. Hennerici, P.J. Kelly, M. Král, H.-F. Lin, C. Molina, J.M. Park, F. Purroy, P.M. Rothwell, T. Segura, D. Školoudík, P.G. Steg, P.-J. Touboul, S. Uchiyama, É. Vicaut, Y. Wang, and L.K.S. Wong, for the TIAregistry.org Investigators*

ABSTRACT

BACKGROUND

After a transient ischemic attack (TIA) or minor stroke, the long-term risk of stroke and other vascular events is not well known. In this follow-up to a report on 1-year outcomes from a registry of TIA clinics in 21 countries that enrolled 4789 patients with a TIA or minor ischemic stroke from 2009 through 2011, we examined the 5-year risk of stroke and vascular events.

METHODS

We evaluated patients who had had a TIA or minor stroke within 7 days before enrollment in the registry. Among 61 sites that participated in the 1-year outcome study, we selected 42 sites that had follow-up data on more than 50% of their enrolled patients at 5 years. The primary outcome was a composite of stroke, acute coronary syndrome, or death from cardiovascular causes (whichever occurred first), with an emphasis on events that occurred in the second through fifth years. In calculating the cumulative incidence of the primary outcome and secondary outcomes (except death from any cause), we treated death as a competing risk.

RESULTS

A total of 3847 patients were included in the 5-year follow-up study; the median percentage of patients with 5-year follow-up data per center was 92.3% (interquartile range, 83.4 to 97.8). The composite primary outcome occurred in 469 patients (estimated cumulative rate, 12.9%; 95% confidence interval [CI], 11.8 to 14.1), with 235 events (50.1%) occurring in the second through fifth years. At 5 years, strokes had occurred in 345 patients (estimated cumulative rate, 9.5%; 95% CI, 8.5 to 10.5), with 149 of these patients (43.2%) having had a stroke during the second through fifth years. Rates of death from any cause, death from cardiovascular causes, intracranial hemorrhage, and major bleeding were 10.6%, 2.7%, 1.1%, and 1.5%, respectively, at 5 years. In multivariable analyses, ipsilateral large-artery atherosclerosis, cardioembolism, and a baseline ABCD^2 score for the risk of stroke (range, 0 to 7, with higher scores indicating greater risk) of 4 or more were each associated with an increased risk of subsequent stroke.

CONCLUSIONS

In a follow-up to a 1-year study involving patients who had a TIA or minor stroke, the rate of cardiovascular events including stroke in a selected cohort was 6.4% in the first year and 6.4% in the second through fifth years. (Funded by AstraZeneca and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Amarenco at the Department of Neurology and Stroke Center, Bichat Hospital, 46 rue Henri Huchard, 75018 Paris, France, or at pierre.amarenco@aphp.fr.

*A complete list of the TIAregistry.org investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 16, 2018, at NEJM.org.

N Engl J Med 2018;378:2182-90.
DOI: 10.1056/NEJMoa1802712

With urgent diagnosis and management of transient ischemic attack (TIA) and minor ischemic stroke and a reduction of risk factors during the past decades, the risk of stroke and other vascular events and stroke has been reduced.[1-3] In previous reports involving patients enrolled in stroke registries from specialized centers,[2] the score on the ABCD[2] (age, blood pressure, clinical findings, duration of symptoms, and presence or absence of diabetes) scale (range, 0 to 7, with higher scores indicating a greater risk of stroke),[4] the presence of a brain lesion on cerebral imaging, and atherosclerotic disease in a major vessel on the side of the affected cerebral hemisphere were significantly associated with the 1-year risk of another stroke.[3] The risk of another event increased during the first 10 days, then was relatively stable for the remainder of the year.[3,5-8] There are few studies of the risk of stroke beyond 1 year among patients who have had a TIA or minor stroke in the modern era of treatment, particularly with the use of thrombolytic agents,[9-11] and many studies addressing the risk of recurrent stroke have been from single centers.

The TIAregistry.org project was designed to prospectively enroll patients with a recent TIA or minor stroke in order to determine the short-term (3-month and 1-year)[3] and long-term (5-year) outcomes. Patients were recruited from 2009 through 2011, in the era when emergency services for TIA and minor stroke had been implemented in the health care systems of many developed countries. The 1-year follow-up of these patients has been reported.[3] We report the 5-year follow-up from a selected group of centers in this registry.

Methods

Study Design and Oversight

The methods of patient recruitment and evaluation for the TIAregistry.org project have been described previously.[3] The protocol, available with the full text of this article at NEJM.org, was approved by local institutional review boards. All the patients provided written or oral informed consent according to country regulation. All the authors vouch for the validity of the data and adherence to the protocol.

The study was supported by unrestricted grants from AstraZeneca, Sanofi, and Bristol-Myers Squibb, none of which had any involvement in the design or conduct of the study, the analysis or interpretation of the data, or the writing of the manuscript. SOS–Attaque Cérébrale Association (a not-for-profit organization) and the Charles Foix Group (an academic research organization for clinical trials in stroke at Université Paris-Diderot, Sorbonne-Paris Cité) were responsible for the conduct of the study.

Study Sites and Population

Patients were eligible for enrollment if they were 18 years of age or older and had had a TIA or minor stroke within the previous 7 days. All the patients were evaluated by stroke specialists. Eligible patients had focal retinal or brain ischemia with resolution of symptoms or minor strokes and a score on the modified Rankin scale (range, 0 to 6, with 0 indicating no symptoms, 1 no disability, and 6 death) of 0 or 1 when first evaluated by stroke specialists.

Sites in the registry from 21 countries had a dedicated system for the care of patients with TIA (with care delivered by stroke specialists). Each site had a yearly volume of at least 100 patients with a TIA or minor stroke during the 3 years before the inception of the study. The sites included emergency departments, stroke units, specialized day clinics, and outpatient clinics, all of which were staffed by stroke specialists and designed to evaluate patients on an urgent basis. Sites with follow-up data on more than 50% of their enrolled patients at 5 years were selected for the analysis in this report, and all reported results pertain to this selected cohort. Of the original 61 sites participating in the 1-year study, 10 had 5-year follow-up data on 0% of patients, 4 had data on 1 to 10%, 1 had data on 16%, 1 had data on 32%, and 1 had data on 44% (2 other sites enrolled patients but never provided any baseline data or follow-up data); the patients in these sites are therefore not included in the current report. These were academic centers distributed among Europe, Asia, and Latin America.

Data regarding the patients were collected prospectively with the use of a Web-based case-report form during face-to-face interviews at the time of evaluation of the qualifying event (baseline); at 1, 3, and 12 months after the initial evaluation; and every 12 months thereafter for 5 years. If the patient could not be reached for follow-up, a relative or the family doctor was interviewed by telephone. At baseline, patients were evaluated

for clinical symptoms, medical history, and socioeconomic factors; a physical examination was performed; and investigations (including brain and cerebral-artery imaging and cardiac evaluation) were recommended. Decisions regarding medical treatment and endovascular revascularization procedures were made by the stroke specialist on the basis of the findings. Patients were evaluated at follow-up for clinical events, medical treatment, and cardiovascular risk factors.

CLINICAL EVENTS AND OUTCOMES

The primary outcome was a composite of death from cardiovascular causes, nonfatal stroke (either ischemic or hemorrhagic), or nonfatal acute coronary syndrome (myocardial infarction with or without ST-segment elevation or unstable angina followed by urgent catheterization), whichever occurred first. Recurrent TIAs were not included in the primary outcome. Any cardiovascular event after the qualifying event (i.e., after the patient first sought medical attention), even if the event occurred before evaluation by a stroke specialist, was considered to be an outcome event. Secondary outcomes included individual components of the primary outcome, TIA recurrence, death from any cause, any bleeding in the brain or elsewhere in the body, and the modified Rankin score at last follow-up.

Ischemic stroke was defined as one of the following: a new symptomatic neurologic deterioration lasting at least 24 hours that was not attributable to a nonischemic cause, or a new symptomatic neurologic deterioration that was not attributable to a nonischemic cause and was accompanied by neuroimaging evidence of a new brain infarction. Hemorrhagic stroke was defined as acute extravasation of blood into the brain parenchyma. Death from cardiovascular causes included fatal acute coronary syndrome, fatal stroke, fatal intracranial hemorrhage, fatal pulmonary embolism, sudden death, and unobserved or unexpected death within 30 days. TIA was defined as new neurologic symptoms or deficit lasting less than 24 hours with no new infarction on neuroimaging. Bleeding was categorized as severe or life-threatening, moderate, or mild according to the Global Utilization of Streptokinase and Tissue Plasminogen Factor for Occluded Coronary Arteries (GUSTO) definitions.[12] Primary outcome events and all bleeding events were adjudicated by two of the investigators on the basis of clinical records.

STATISTICAL ANALYSIS

We initially calculated that a sample size of 5000 would allow a 10% relative precision in the estimate of the rate of the primary outcome after a maximum follow-up of 5 years (corresponding to an accrual time of 4 years and a minimal follow-up period of 1 year), assuming an average annual risk of composite events of 2.5%. Because we intended to follow all the patients for 5 years and to perform a short-term analysis at the 1-year follow-up, we used the Peto method for calculating the standard error of survival at the given time to determine that with a 25% attrition rate at 5 years, the relative precision of the estimates of the composite event rate would be 18% at 1 year and 9% at 5 years.

Continuous variables are expressed as means and standard deviations or medians and interquartile ranges, and categorical variables are expressed as frequencies and percentages. To assess the representativeness of the study sample from the initial sample, we described the main baseline characteristics of the patients who were included in the sample and those who were not included. The magnitude of the between-group differences was assessed by calculating the standardized differences, and an absolute standardized difference of more than 0.20 was interpreted as a meaningful difference. We calculated the length of follow-up on the basis of the reverse Kaplan–Meier estimator[13] of overall survival.

In the analysis of the cumulative incidence of the primary outcome and secondary outcomes (except death from any cause), we used the approach of Kalbfleisch and Prentice by treating death as a competing risk.[14] The probability of the rate of death from any cause was estimated by the Kaplan–Meier method. Data for patients with no information at 5 years were censored at the time of the last available follow-up. Events that occurred after the 5-year follow-up period were not included in this analysis. Event rates were estimated among the overall study sample (main analysis), among patients evaluated by a stroke specialist within 24 hours after symptom onset (prespecified sensitivity analysis), and among patients from the 33 sites with follow-up data on

more than 80% of their patients at 5 years (post hoc sensitivity analysis).

The ABCD^2 score, acute infarctions on brain imaging, and the probable cause of the initial TIA or minor stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification have been shown to be associated with stroke recurrence. Thus, we used a Fine–Gray model[14] to assess the prognostic values of these factors on stroke recurrence from a 1-year period to a 5-year period, using a landmark analysis at 1 year for these prognostic factors. The proportional-hazards assumption was verified with the use of Schoenfeld residuals. Owing to missing data on the ABCD^2 score, acute infarction lesions, and TOAST classification, we performed a multivariable analysis with multiple imputation of missing values by means of chained equations (10 imputations; see the Methods section in the Supplementary Appendix, available at NEJM.org, for further details). A sensitivity analysis was performed on complete case data (Fig. S5 in the Supplementary Appendix).

Statistical testing was conducted at a two-tailed alpha level of 0.01 to account for multiple comparisons. Data were analyzed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

BASELINE DATA AND SELECTION OF PATIENTS

From June 2009 through December 2011, a total of 61 sites in 21 countries enrolled 4789 patients in the TIAregistry.org project. Of the 61 sites, 42 had follow-up data on more than 50% of their patients at 5 years (3847 patients), who represented 80.3% of the initial cohort (Fig. S1 in the Supplementary Appendix). The median percentage of patients with 5-year follow-up data in these selected centers was 92.3% (interquartile range, 83.4 to 97.8), with a total of 3356 patients (87.2%) with all data available for analysis in this report.

Follow-up at 5 years was by face-to-face interview in 46.2% of patients and by telephone call in 47.5%; the remainder of the patients had died or were lost to follow-up (Table S1 in the Supplementary Appendix). Table 1, and Table S2 in the Supplementary Appendix, show the baseline characteristics and missing data of the cohort who had 5-year follow-up data. A comparison between the patients who were included in this analysis and

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Value
Evaluated by stroke specialist within 24 hr after symptom onset — no./total no. (%)	2971/3847 (77.2)
Age — yr	66.4±13.2
Male sex — no./total no. (%)	2295/3841 (59.8)
Medical history — no./total no. (%)	
Hypertension	2704/3845 (70.3)
Diabetes	726/3845 (18.9)
Dyslipidemia	2708/3845 (70.4)
Former smoker	942/3801 (24.8)
Current smoker	835/3801 (22.0)
Stroke or TIA	649/3836 (16.9)
Coronary artery disease	481/3833 (12.5)
Peripheral artery disease	113/3819 (3.0)
Atrial fibrillation or flutter	335/3836 (8.7)
Modified Rankin score — no./total no. (%)†	
0	2579/3821 (67.5)
1	1209/3821 (31.6)
ABCD^2 score — no./total no. (%)‡	
0–3	1103/3417 (32.3)
4–5	1641/3417 (48.0)
>5	673/3417 (19.7)
Body-mass index	26.3±4.6
Blood pressure — mm Hg	
Systolic	146±24
Diastolic	81±13
Glucose — mg/dl	
Median	103
Interquartile range	90–129
Cholesterol — mg/dl	
LDL	119±41
HDL	51±16

* Plus–minus values are means ±SD. Data were missing for 35 patients for age, 504 patients for body-mass index (the weight in kilograms divided by the square of the height in meters), 300 patients for systolic blood pressure, 301 patients for diastolic blood pressure, 532 patients for glucose level, 890 patients for low-density lipoprotein (LDL) cholesterol level, and 853 patients for high-density lipoprotein (HDL) cholesterol level. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for glucose to millimoles per liter, multiply by 0.05551. TIA denotes transient ischemic attack.

† Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no disability, and 6 death.

‡ Scores on the ABCD^2 (age, blood pressure, clinical findings, duration of symptoms, and presence or absence of diabetes) scale range from 0 to 7, with higher scores indicating a greater risk of stroke.

Table 2. Medication Use, Atrial Fibrillation, and Surgery at Baseline, Discharge, 1 Year, and 5 Years.

Variable	Before Admission (N=3847)	At Discharge (N=3847)	At 1 Year (N=3565)	At 5 Years (N=2948)
	number/total number (percent)			
≥1 Antiplatelet agent	1063/3831 (27.7)	3410/3762 (90.6)	2742/3515 (78.0)	1923/2705 (71.1)
Aspirin	925/1063 (87.0)	2538/3410 (74.4)	1981/2742 (72.2)	1347/1923 (70.0)
Other antiplatelet agent	243/1063 (22.9)	1347/3410 (39.5)	1072/2742 (39.1)	702/1923 (36.5)
Dual antiplatelet therapy	108/1063 (10.2)	550/3410 (16.1)	316/2742 (11.5)	127/1923 (6.6)
≥1 Anticoagulant agent	191/3832 (5.0)	614/3781 (16.2)	601/3499 (17.2)	461/2704 (17.0)
≥1 Antihypertensive agent	2114/3838 (55.1)	2621/3815 (68.7)	2477/3484 (71.1)	1904/2701 (70.5)
1	879/2114 (41.6)	1155/2621 (44.1)	998/3484 (28.6)	752/1904 (39.5)
2	691/2114 (32.7)	785/2621 (30.0)	853/3484 (24.5)	686/1904 (36.0)
≥3	497/2114 (23.5)	550/2621 (21.0)	618/3484 (17.7)	461/1904 (24.2)
≥1 Lipid-lowering agent	1064/3834 (27.8)	2674/3793 (70.5)	2362/3483 (67.8)	1728/2704 (63.9)
Statin	987/1064 (92.8)	2583/2674 (96.6)	2293/2362 (97.1)	1680/1728 (97.2)
Other lipid-lowering agent	114/1064 (10.7)	110/2674 (4.1)	118/2362 (5.0)	121/1728 (7.0)
≥1 Glucose-lowering agent	637/3831 (16.6)	714/3789 (18.8)	586/3391 (17.3)	479/2700 (17.7)
Carotid endarterectomy*		96/3847 (2.5)	172/3847 (4.5)	191/3847 (5.0)
Carotid endarterectomy since discharge			76/3565 (2.1)	19/2948 (0.6)
Atrial fibrillation*		370/3847 (9.6)	442/3847 (11.5)	509/3847 (13.2)
New onset of atrial fibrillation since discharge			72/3565 (2.0)	67/2948 (2.3)
Anticoagulant agent for atrial fibrillation	130/331 (39.3)	241/367 (65.7)	52/72 (72.2)	47/67 (70.1)

* Shown are cumulative frequencies at the different time points.

the 736 patients from the initial 1-year cohort who were not included in the 5-year analysis is shown in Table S3 in the Supplementary Appendix. Patients who were not included in the 5-year analysis had lower rates of hypertension, dyslipidemia, and current smoking status than those who were included, and they had lower scores on the modified Rankin scale (signifying less disability from the initial strokes), lower scores on the National Institutes of Health Stroke Scale (signifying less severe initial strokes), and lower ABCD^2 scores (signifying better predicted prognosis for recurrence of stroke).

TREATMENT MANAGEMENT DURING FOLLOW-UP

Rates of medication use at hospital discharge after the first stroke and at 5 years were as follows: blood-pressure–lowering therapy, 68.7% and 70.5%, respectively; lipid-lowering therapy, 70.5% and 63.9%; glucose-lowering therapy, 18.8% and 17.7%; antiplatelet therapy, 90.6% and 71.1%; and anticoagulant therapy, 16.2% and 17.0% (Table 2). At 5 years, the mean blood pressure was 132/77 mm Hg, and the mean level of low-density lipoprotein (LDL) cholesterol was 92 mg per deciliter (2.38 mmol per liter); the median LDL level was 86 mg per deciliter (interquartile range, 69 to 108) (2.22 mmol per liter; interquartile range, 1.78 to 2.79) (Figs. S2 and S3 in the Supplementary Appendix). Of 835 active smokers (22.0% of 3801 patients) at baseline, 388 (10.2%) were still active smokers at 1 year and 292 (7.7%) at 5 years.

OUTCOME EVENTS

At the time of database closure on August 16, 2017, the median follow-up was 5.01 years (interquartile range, 4.84 to 5.26). At year 5, a primary outcome event had occurred in 469 patients (death from a cardiovascular cause in 96 patients, a nonfatal stroke in 297, and a nonfatal acute coronary syndrome in 76), corresponding to an estimated cumulative event rate of 12.9% (95% confidence interval [CI], 11.8 to 14.1) (Table 3). A total of 235 of the events (50.1%) occurred during years 2 through 5. Absolute event rates

were 6.4% in the first year and 6.4% in the second through fifth years. Stroke occurred in 345 patients during the 5-year period (a primary outcome event of fatal stroke occurred in 44), with 149 of these 345 patients (43.2%) having had a stroke during years 2 through 5. At 5 years, myocardial infarction had occurred in 39 patients. Figure 1 shows that the Kaplan–Meier estimate of the probability of primary outcome events continued to increase after the first year.

Death from any cause occurred in 373 patients (estimated rate, 10.6%), any recurrent stroke or TIA in 621 (16.8%), any acute coronary syndrome in 84 (2.4%), and any major bleeding in 53 (1.5%). Intracranial hemorrhage occurred in 39 patients (1.1%), of whom 15 (38%) were receiving anticoagulant therapy (representing 3.3% of the 461 patients receiving anticoagulant therapy), 16 (41%) were receiving antiplatelet monotherapy (representing 0.9% of the 1784 patients receiving antiplatelet monotherapy), and 5 (13%) were receiving dual antiplatelet therapy (representing 3.9% of the 127 patients receiving dual antiplatelet therapy). As a post hoc measure of disability caused by a recurrent stroke, a combination of the primary outcome and a modified Rankin score of more than 1 (indicating some degree of neurologic disability) occurred in 299 patients, with an event rate of 7.9% (95% CI, 7.1 to 8.9) (Table S4 and Fig. S4 in the Supplementary Appendix).

SENSITIVITY ANALYSIS

In a sensitivity analysis restricted to patients enrolled within 24 hours after symptom onset (77.2% of the patients in this analysis), a primary outcome event had occurred in 13.4% of the patients (95% CI, 12.1 to 14.7) at 5 years (Table S5 in the Supplementary Appendix). A sensitivity analysis that was restricted to 33 centers (2897 patients) with follow-up data on more than 80% of their patients at 5 years (median, 95.4%; 95% CI, 90.0 to 98.2) showed an event rate of 13.3% (95% CI, 12.1 to 14.6) (Table S6 in the Supplementary Appendix). Among the potential causes of qualifying TIA or minor stroke that were considered in the 1-year report,[3] ipsilateral large-artery atherosclerosis, cardioembolism, and an ABCD^2 score of 4 or more, but not the presence of a brain lesion on neuroimaging, were independent predictors of recurrent stroke during years 2 through 5 (Fig. 2, and Fig. S5 in the Supplementary Appendix).

Table 3. Event Rates at 5 Years.

Outcome	Patients (N = 3847)	
	no.	*% (95% CI)**
Primary outcome†		
Major cardiovascular events	469	12.9 (11.8–14.1)
Death from cardiovascular cause	96	2.7 (2.2–3.3)
Fatal stroke	44	1.1 (0.8–1.6)
Fatal myocardial infarction	3	0.1 (0.0–0.2)
Nonfatal stroke	297	8.1 (7.3–9.0)
Nonfatal acute coronary syndrome	76	2.1 (1.7–2.6)
Secondary outcomes‡		
Death from any cause	373	10.6 (9.6–11.7)
Death from cardiovascular cause	96	2.7 (2.2–3.3)
Fatal stroke	44	1.1 (0.8–1.6)
Fatal myocardial infarction	3	0.1 (0.0–0.2)
Stroke or TIA	621	16.8 (15.6–18.1)
Stroke	345	9.5 (8.5–10.5)
TIA	307	8.3 (7.4–9.2)
Intracranial hemorrhage	39	1.1 (0.7–1.5)
Acute coronary syndrome	84	2.4 (1.8–2.9)
Myocardial infarction	39	1.1 (0.8–1.6)
Bleeding	230	6.5 (5.6–7.3)
Moderately severe§	52	1.5 (1.1–1.9)
Major¶	53	1.5 (1.1–2.0)

* In the analysis of the cumulative incidence of the primary outcome and secondary outcomes (except death from any cause), we used the approach of Kalbfleisch and Prentice by treating death as a competing risk.[14] The rate of death from any cause was estimated by the Kaplan–Meier method.

† The primary outcome was a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal acute coronary syndrome, whichever occurred first. Therefore, a patient could have no more than one primary outcome event.

‡ Patients with multiple events during the 5-year period may be classified as having different secondary outcomes. One patient could have several events: 31 patients had both a stroke and a TIA; 4 patients had an acute coronary syndrome before a recurrent stroke.

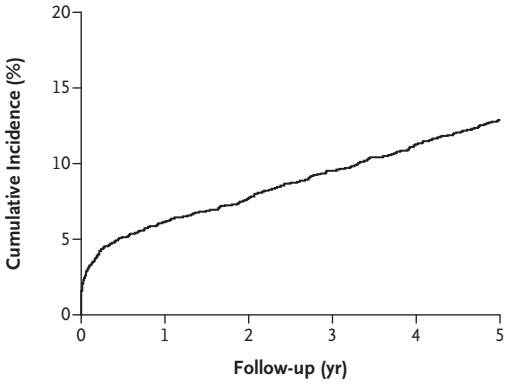
§ Moderately severe bleeding was defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Factor for Occluded Coronary Arteries (GUSTO) definition: bleeding that requires transfusion of blood but does not lead to hemodynamic compromise requiring intervention.

¶ Major bleeding was defined according to the GUSTO definition for severe bleeding: documented intracranial hemorrhage or bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assistance devices, surgical intervention (other than vascular site repair), or cardiopulmonary resuscitation to maintain a sufficient cardiac output.

DISCUSSION

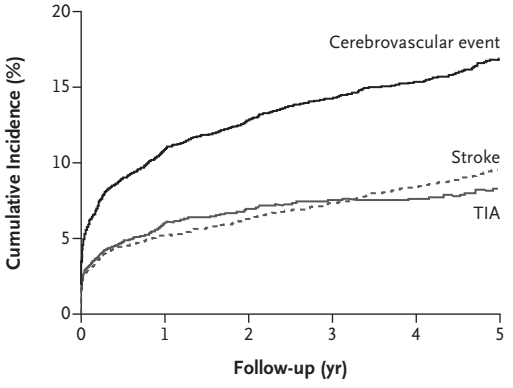
In this registry-based analysis of patients with a TIA or minor stoke in a selected cohort represent-

A Major Cardiovascular Events



No. of Patients						
Alive and free of event	3847	3471	3216	3006	2833	2197
Event	0	235	290	358	415	469
Death from nonvascular causes	0	48	97	148	198	249

B Cerebrovascular Events, Stroke, and TIA



No. of Patients						
Cerebrovascular event						
Alive and free of event	3847	3291	3028	2825	2664	2066
Event	0	410	481	533	570	621
Death from nonvascular causes	0	54	105	170	231	287
Stroke						
Alive and free of event	3847	3501	3254	3057	2889	2252
Event	0	196	235	271	309	345
Death from nonvascular causes	0	57	114	182	247	303
TIA						
Alive and free of event	3847	3451	3201	3022	2872	2240
Event	0	225	262	280	286	307
Death from nonvascular causes	0	73	138	210	283	350

Figure 1. Kaplan–Meier Event Curves at 5 Years.

Panel A shows the cumulative incidence of the composite primary outcome (stroke, acute coronary syndrome, or death from cardiovascular causes) in the overall population over a period of 5 years. Panel B shows the cumulative incidence of any cerebrovascular event, any stroke, and transient ischemic attack (TIA).

ing 80% of an initial cohort previously reported with 1-year outcomes, there was a risk of a composite outcome of stroke, acute coronary syndrome, or death from cardiovascular causes of 12.9% at 5 years and a risk of stroke of 9.5%, approximately twice the rates of 6.2% and 5.1%, respectively, reported at 1 year.[3] These rates were lower than the rates of 22% and 17%, respectively, in historical cohorts before the widespread adoption of aggressive risk-reduction measures for vascular disease.[5,6,15] Half the primary outcome events in the current report occurred during years 2 through 5, which raises the question of whether preventive strategies could decrease the risk of stroke after a TIA or a minor ischemic stroke beyond 1 year. To measure the effect of minor stroke on disability, we performed a post hoc analysis of the 5-year risk of the primary outcome and a modified Rankin score of more than 1 (signifying the presence of a neurologic deficit), and 7.9% of the patients had a deficit or had died. Measures such as this one that include the residual effect of strokes may be useful outcomes in clinical trials. Our study did not include TIA as a primary outcome because of ambiguities in making this diagnosis at follow-up visits.

Our registry was composed primarily of patients at moderate-to-high risk for stroke, as more than two thirds of the cohort had an ABCD^2 score of 4 or more at the time of their first stroke (Table 1). Among stroke subtypes leading to enrollment in the registry, ipsilateral atherosclerotic stenosis, a cardiac source of embolism (mainly atrial fibrillation), and small-vessel disease were predictors of recurrent stroke during years 2 through 5. These results are consistent with the finding in our 1-year outcome study and other reports that atherosclerotic stenosis ipsilateral to the original stroke confers the highest risk of recurrence, even beyond 1 year.[3,15,16] An ABCD^2 score of 4 or more at baseline was predictive of the risk of recurrent stroke during years 2 through 5, whereas a baseline brain lesion on neuroimaging was predictive of the risk of stroke at 1 year[3] but not during years 2 through 5 (Fig. 2).

Of 3847 patients who were evaluated for the 5-year study, 3356 (87.2%) had complete 5-year follow-up data available. This follow-up rate affects the confidence intervals around point estimates of events and may underestimate the rates

Subgroup	Total No. of Patients	No. of Patients with Stroke Recurrence (%)	Hazard Ratio for Stroke Recurrence (95% CI)	P Value
TOAST classification				
Undetermined cause	1180	29 (2.7)	1.00 (reference)	—
Large-artery atherosclerosis	829	51 (6.5)	2.30 (1.40–3.76)	0.001
Small-vessel occlusion	746	31 (4.6)	1.51 (0.87–2.61)	0.14
Cardioembolism	548	30 (5.9)	2.13 (1.22–3.70)	0.007
Other determined cause	198	8 (5.0)	2.01 (0.90–4.48)	0.09
Findings on brain imaging				
No acute infarction	2309	95 (4.5)	1.00 (reference)	—
Single acute infarction	834	38 (5.0)	0.97 (0.65–1.45)	0.89
Multiple acute infarctions	358	16 (4.8)	0.82 (0.47–1.42)	0.47
ABCD^2 score				
0–3	1166	30 (2.9)	1.00 (reference)	—
4–5	1682	85 (5.5)	1.82 (1.14–2.89)	0.01
6–7	653	34 (5.7)	1.78 (1.03–3.05)	0.04

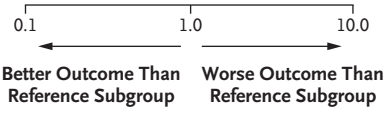


Figure 2. Subgroup Analysis.

Shown are event rates and multivariate hazard ratios for stroke recurrence according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, initial findings on brain imaging, and the score on the ABCD^2 (age, blood pressure, clinical findings, duration of symptoms, and presence or absence of diabetes) scale (range, 0 to 7, with higher scores indicating a greater risk of stroke) after 1 year (landmark analysis, 3501 patients) after multiple imputation for missing data. The reference subgroups for the hazard ratios are a TOAST classification of ischemic stroke of undetermined cause, no acute infarction on brain imaging, and an ABCD^2 score of 0.3. The number of patients with stroke recurrence is the cumulative incidence at 5 years after inclusion (4 years after the landmark time), as estimated by considering death not caused by stroke as a competing risk. Event rates for stroke recurrence are for years 2 through 5.

of these events. Furthermore, only 10% of the data were audited for accuracy at all three time points of baseline, 1 year, and 5 years. In addition, there were differences in risk factors between the patients in the initial 1-year cohort and the cohort with 5-year outcome data. Although primary outcome events and major bleeding events were adjudicated, all the limitations named above may also have led to underreporting of these events. Taken together, and given the specialized nature of the sites in the registry, these patients are different from those in population-based studies of stroke but may represent patients who would be included in clinical trials.

In conclusion, among patients who had had a TIA or minor stroke, we observed a sustained risk of cardiovascular events over a period of 5 years, with half of the events occurring during years 2 through 5. There may be potential for reducing recurrent strokes by ongoing secondary prevention measures.

Supported by unrestricted grants from AstraZeneca, Sanofi, and Bristol-Myers Squibb.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Pierre Amarenco, M.D., Philippa C. Lavallée, M.D., Linsay Monteiro Tavares, B.S.T., Julien Labreuche, B.S.T., Gregory W. Albers, M.D., Halim Abboud, M.D., Sabrina Anticoli, M.D., Heinrich Audebert, M.D., Natan M. Bornstein, M.D., Louis R. Caplan, M.D., Manuel Correia, M.D., Geoffrey A. Donnan, M.D., José M. Ferro, M.D., Fernando Gongora-Rivera, M.D., Wolfgang Heide, M.D., Michael G. Hennerici, M.D., Peter J. Kelly, M.D., Michal Král, M.D., Hsiu-Fen Lin, M.D., Carlos Molina, M.D., Jong Moo Park, M.D., Francisco Purroy, M.D., Peter M. Rothwell, M.D., Tomas Segura, M.D., David Školoudík, M.D., Ph.D., P. Gabriel Steg, M.D., Pierre-Jean Touboul, M.D., Shinichiro Uchiyama, M.D., Éric Vicaut, M.D., Yongjun Wang, M.D., and Lawrence K.S. Wong, M.D.

The authors' affiliations are as follows: Assistance Publique–Hôpitaux de Paris (AP-HP), Department of Neurology and Stroke Center (P.A., P.C.L., L.M.T., J.L., P.-J.T.), and the Department of Cardiology (P.G.S.), Bichat Hospital, INSERM Laboratory for Vascular Translational Science–Unité 1148, Département Hospitalo-Universitaire Fibrose Inflammation Remodelage, Université Paris-Diderot, Sor-

bonne-Paris Cité, and AP-HP, Department of Biostatistics, Université Paris-Diderot, Sorbonne-Paris Cité, Fernand Widal Hospital (É.V.), Paris, and Université Lille, Centre Hospitalier Universitaire Lille, Équipe d'Accueil 2694–Santé Publique: Épidémiologie et Qualité des Soins, Lille (J.L.) — all in France; the Stanford Stroke Center, Department of Neurology and Neurological Sciences, Stanford University Medical Center, Stanford, CA (G.W.A.); the Department of Neurology, Hôtel-Dieu de France, Saint Joseph University, Beirut, Lebanon (H. Abboud); the Stroke Unit, San Camillo Hospital, Rome (S.A.); Ärztliche Leitung der Klinik für Neurologie, Campus Benjamin Franklin, Charité–Universitätsmedizin Berlin, Berlin (H. Audebert), Klinik für Neurologie, Allgemeines Krankenhaus Celle, Celle (W.H.), and the Department of Neurology, Universitäts Medizin Mannheim, Heidelberg University, Heidelberg (M.G.H.) — all in Germany; Shaare Zedek Medical Center, Jerusalem, Israel (N.M.B.); the Cerebrovascular Disease Service, Beth Israel Deaconess Medical Center, Harvard University, Boston (L.R.C.); Serviço de Neurologia, Hospital de Santo António–Centro Hospitalar do Porto, Porto (M.C.), and the Department of Neurosciences, Service of Neurology, Hospital Santa Maria, University of Lisbon, Lisbon (J.M.F.) — both in Portugal; the Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC, Australia (G.A.D.); the Stroke Unit and Neurology Service, University Hospital José Eleuterio González, Universidad Autónoma de Nuevo León, Monterrey, Mexico (F.G.-R.); the Neurovascular Research Unit and Health Research Board, Stroke Clinical Trials Network Ireland, University College Dublin, Dublin (P.J.K.); the Comprehensive Stroke Center, Palacký University and University Hospital Olomouc (M.K.), and the Department of Nursing, Faculty of Health Science, Palacký University (D.Š), Olomouc, Czech Republic; the Department of Neurology, Kaohsiung Medical University Chung-Ho Memorial Hospital and Kaohsiung Medical University, Kaohsiung, Taiwan (H.-F.L.); the Stroke Unit, Department of Neurology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona (C.M.), the Stroke Unit, Hospital Universitari Arnau de Vilanova, Universitat de Lleida, Lleida (F.P.), and the Stroke Unit, Department of Neurology, Albacete University Hospital, Universidad de Castilla–La Mancha, Albacete (T.S.) — all in Spain; the Department of Neurology, Nowon Eulji Medical Center, Eulji University, Seoul, South Korea (J.M.P.); the Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford (P.M.R.), and the National Heart and Lung Institute Imperial College, Institute of Cardiovascular Medicine and Science Royal Brompton Hospital, London (P.G.S.) — both in the United Kingdom; the International University of Health and Welfare, Center for Brain and Cerebral Vessels, Sanno Hospital and Sanno Medical Center, Tokyo (S.U.); the Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing (Y.W.); and the Department of Medicine and Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong (L.K.S.W.).

REFERENCES

1. Lavallée PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol 2007;6:953-60.
2. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007;370:1432-42.
3. Amarenco P, Lavallée PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor ischemic stroke. N Engl J Med 2016;374:1533-42.
4. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283-92.
5. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901-6.
6. Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. Stroke 2003;34(8):e138-e140.
7. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11-9.
8. Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus aspirin in acute ischemic stroke or transient ischemic attack. N Engl J Med 2016;375:35-43.
9. Clark TG, Murphy MF, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in "low risk" patients with a non-recent transient ischaemic attack. J Neurol Neurosurg Psychiatry 2003;74:577-80.
10. Luengo-Fernandez R, Paul NL, Gray AM, et al. Population-based study of disability and institutionalization after transient ischemic attack and stroke: 10-year results of the Oxford Vascular Study. Stroke 2013;44:2854-61.
11. Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. Neurology 2013;81:1588-95.
12. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
13. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343-6.
14. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
15. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457-507.
16. Amarenco P, Albers GW, Denison H, et al. Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. Lancet Neurol 2017;16:301-10.